Ontario College of Family Physicians - 51st Annual Scientific Assembly

**WHAT:** Genomics and Primary Care: Are you prepared?

**WHEN:** Thursday November 28th, 2013, 13:30-15:00

**WHO:** Dr. June C Carroll, MD, CCFP, FCFP, Dr. Judith Allanson MB ChB FRCP(C), FCCMG, Dr. Sean Blaine MD CCFP FCFP, Ms. Shawna Morrison MS, CGC

Enclosed are five concise, evidenced-based fact sheets, “GEC-KO on the run”, on the following genomic topics:

- Hereditary Hemochromatosis (HH)
- Lynch Syndrome (LS)
- Chromosomal Microarray (CMA)
- Non-invasive Prenatal Testing (NIPT)
- Direct-to-Consumer genetic testing (DTC-GT)

Additional information can be found at [www.gecko-cegco.ca](http://www.gecko-cegco.ca) or for further questions regarding the handouts please contact GEC-KO’s program manager, Shawna Morrison, at [morrison@cheo.on.ca](mailto:morrison@cheo.on.ca)
HEREDITARY HEMOCROMATOSIS (HH)

**Bottom line:** HH is a common inherited predisposition to absorb excess iron from the diet caused by mutations in the *HFE* gene. Most individuals with the predisposition do not develop clinical disease. HH has the potential to cause morbidity and mortality. **With early identification of at-risk individuals, appropriate surveillance of iron indices, and treatment when indicated, all complications can be avoided.**

Genetic testing should be considered for:

- Adults with biochemical evidence of iron overload (>45% fasting transferrin saturation and >300µg/L serum ferritin in men and post-menopausal women or >200µg/L SF in pre-menopausal women)
- Any adult whose first-degree relative has the C282Y HFE gene mutation

**WHAT IS HH?**

Hereditary Hemochromatosis (HH) is an autosomal recessive predisposition to absorb excess iron from the diet. The most common cause of HH is mutations in the *HFE* gene disrupting the iron absorption pathway. In some predisposed individuals, excessive iron absorption and subsequent storage in various organs (i.e. liver, pancreas, heart, joints) eventually lead to cellular injury. If untreated, over time this can cause irreversible tissue/organ damage and shorten life expectancy. Typically, symptoms of *HFE*-HH present in men aged 40 to 60 and in post-menopausal women; however, age of onset is variable. Symptoms are non-specific and include weakness, lethargy, skin discoloration (bronze or grey), abdominal pain with or without hepatomegaly, joint pain and/or stiffness, arthritis, diabetes, cardiomyopathy, hepatocellular dysfunction, cirrhosis, hepatocellular carcinoma, testicular atrophy, impotence, and menstrual irregularity. While any of these health concerns can be caused by *HFE*-HH, the presence of two or more should greatly increase suspicion that the condition is present. Iron overload due to *HFE* mutations does not occur in childhood, and as HH is an adult onset predisposition, genetic testing in children is not recommended.

**With early identification of at-risk individuals, appropriate surveillance of iron indices, and treatment when necessary, all complications can be avoided.**

Standard testing by North American molecular genetics laboratories is targeted mutation analysis to look specifically for the two most common *HFE* mutations, C282Y and H63D. These mutations account for over 90% of all mutations found.

**RED FLAGS TO CONSIDER GENETIC TESTING OR GENETIC CONSULTATION**

A patient with:

- Biochemical evidence of iron overload (>45% fasting transferrin saturation (TS) and >300µg/L serum ferritin (SF) in men and post-menopausal women or >200µg/L SF in pre-menopausal women.)
- Biochemical evidence of iron overload will be present before the onset of symptoms.
- Unexplained chronic liver disease and increased transferrin saturation

*Elevation of ferritin alone is not necessarily due to iron overload. Ferritin is an acute phase reactant and can be elevated due to infection, inflammation and malignancy.*

*Individuals with HFE-HH occasionally demonstrate a normal TS and an elevated ferritin. If clinical suspicion is high and/or the patient has a family history of HFE-HH, genetic testing is still warranted.*
 FAMILY HISTORY RED FLAGS TO CONSIDER GENETIC TESTING

- Adult patient with a first-degree relative (sibling, parent or child) with one of the following genetic test results:
  a. C282Y/C282Y (homozygote - 2 mutated copies of the gene)
  b. C282Y/H63D (compound heterozygote - 2 different mutated copies of the gene)
  c. C282Y/S65C (compound heterozygote)
  d. C282Y heterozygote (carrier - 1 mutated copy of the gene)
- Family history of iron overload, liver disease, type II diabetes, arthritis, heart disease (relatives with symptoms of HFE-HH)

PREVALENCE

About 1 in 3 individuals of northern European ancestry are carriers (heterozygotes) of the C282Y or H63D HFE gene mutation. About 1 in 260 individuals have two copies of (are homozygous for) the C282Y HFE gene mutation (genotype C282Y/C282Y). The prevalence of HFE-HH in other ethnicities is lower.

WHAT DOES THE GENETIC TEST RESULT MEAN?

The actual risk to develop iron overload is dependent on how many and which gene mutations have been inherited, in addition to other genetic and non-genetic factors (gender, alcohol intake, the use of iron and vitamin C supplements and menstrual/pregnancy-associated iron losses).

- Two mutations identified confirm the HFE-HH diagnosis in an individual with biochemical evidence of iron overload.
- Two mutations identified in an asymptomatic individual with normal iron indices suggest future potential risk of developing iron overload. Yearly monitoring of iron indices is recommended.

<table>
<thead>
<tr>
<th>HFE mutations identified</th>
<th>Risk of iron overload</th>
<th>Recommendation</th>
</tr>
</thead>
</table>
| C282Y/C282Y              | Highest risk of developing iron overload (38-50%); nonetheless, many of these individuals never accumulate enough iron to cause disease. About 10-33% may develop HH-related symptoms. That risk is likely higher for those identified through family screening versus those identified through population based screening. | • Annual monitoring of TS and SF  
  • Elevated: >45% TS and >300 μg/L SF in men and post-menopausal women, or >200 μg/L SF in pre-menopausal women |
| C282Y/H63D               | About a 2% lifetime risk of developing iron overload | |
| C282Y/S65C               | Low lifetime risk of developing iron overload - similar to C282Y/H63D | |
| H63D/H63D               | About a 1% lifetime risk of developing iron overload | |

See www.gecko-cego.ca for the full-length GEC-KO Messenger on HFE-HH and how to connect to your local genetics centre or molecular genetics laboratory.

For guidelines on the management of patients with HH, see Bacon et al., Diagnosis and management of hemochromatosis: 2011 practice guideline by the American Association for the Study of Liver Diseases. Hepatology. 54:328–43

Authors: S Morrison MS CGC, JC Carroll MD CCFP and JE Allanson MD FRCPC

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Lynch Syndrome (LS)

**Bottom line:** Lynch syndrome (LS), also known as Hereditary Non-Polyposis Colorectal Cancer syndrome (HNPCC), is the most common hereditary colon cancer predisposition syndrome. It is an autosomal dominant condition that results in an increased lifetime risk of colorectal cancer (CRC) in addition to other cancers. Individuals at high or intermediate risk of LS should be referred for a genetic consultation for consideration of genetic testing. Surveillance and management of CRC and other cancers should be guided by genetic test results and/or family/personal history. Studies show that conversations between patients and their healthcare providers are the strongest driver of screening participation.

**What is Lynch Syndrome?**
Lynch syndrome (LS) is an autosomal dominant cancer predisposition syndrome caused by inherited mutations in genes responsible for correcting DNA replication errors, mismatch repair (MMR) genes. Individuals with LS have a greatly increased risk for certain cancers (Box 1 and Table 1). One to 3% of CRC is attributable to LS. Not all individuals who inherit a mutation in a LS gene will develop cancer (reduced penetrance) and the signs and symptoms, type and age of onset of cancer will vary between affected family members (variable expressivity).

**Box 1: Lynch Syndrome-related cancers**
- Colorectal cancer
- Gastric
- Small bowel
- Brain
- Endometrial
- Ovarian
- Hepatobiliary
- Pancreatic
- Kidney
- Ureter
- Sebaceous (adenoma or carcinoma)

**Prevalence**
About 1 in 440 individuals are estimated to have inherited a mutation in a LS gene.

**Personal History Red Flags to Consider Genetic Testing or Genetic Consultation**
These are general guidelines to identify patients at increased risk for LS. You should check with your local genetics centre or hereditary cancer program for more specific details. Consider referring your patient if they have:
- An early age of CRC diagnosis (<50 years). Patients diagnosed <35 years are much more likely to have LS.
- An early age of endometrial cancer diagnosis (<50 years)
- Multiple primary LS-related cancer diagnoses, regardless of age
- CRC diagnosis with one or more 1st degree relatives with a LS-related cancer, with one of the cancers being diagnosed <50 years
- CRC diagnosis with two or more 1st or 2nd degree relatives with LS-related cancers regardless of age
- CRC diagnosis <60 years with histological features suspicious for LS (excess infiltrating lymphocytes, mucinous/signet cell features, Crohn-like reaction), particularly when primary tumour is right-sided
FAMILY HISTORY RED FLAGS TO CONSIDER GENETIC CONSULTATION

Check with your local genetics centre or hereditary cancer program for specific details.

A patient is considered to be at high risk for LS syndrome if he/she has:

- At least three relatives with a LS-associated cancer (see Box 1); the following criteria should also be present:
  - One must be a first degree relative of the other two;
  - At least two successive generations must be affected (autosomal dominant inheritance);
  - At least one relative with LS-related cancer should be diagnosed before age 50;

*Tumour pathology should be verified when possible and other CRC syndromes should be ruled out.*

A patient is considered to be at intermediate risk for LS if he/she has:

- A 1st or 2nd degree relative with CRC diagnosed before age 35
- A 1st or 2nd degree relative with two or more LS-related cancers (Box 1)
- 2 or more 1st or 2nd degree relatives on the same side of the family with CRC diagnosed before age 50
- 3 or more relatives on the same side of the family with any LS-related cancer diagnosed at any age, at least one of whom has CRC or endometrial cancer

WHAT DOES THE GENETIC TEST RESULT MEAN?

If your patient has been found to carry a mutation in a LS gene, he/she has an increased lifetime risk to develop certain cancers (Table 1 and Box 1). This also means that family members are at risk of carrying the same mutation and of having similar cancer risks. Evidence is emerging from population based studies that these cancer risks are gene specific.

The algorithm for LS testing ideally begins with immunohistochemical (IHC) analysis of a CRC tumour (it is possible to test other tumour types if a CRC tumour is not available) for the most common proteins associated with LS (MLH1, MSH2, MSH6 and PMS2). IHC analysis demonstrates whether the protein product expressed by a gene is intact or deficient. If IHC analysis reveals deficiency of a protein, genetic testing can be offered to the affected individual and performed on a blood sample. If IHC analysis does not clearly show deficient expression of a protein, the next step is microsatellite instability (MSI) testing of the tumour sample. If MSI is stable or low, no further testing is indicated. If MSI is high, genetic testing can be offered to the affected individual and performed on a blood sample.

What is Microsatellite Instability (MSI)?

A microsatellite is an area of DNA with a repetitive sequence (i.e. CGCGCGCGC or GAAGAAGAA). These stretches of DNA are susceptible to acquiring errors when a mutation in a MMR gene is present. Cancer arising as the result of a defective MMR gene exhibits an inconsistent number of microsatellite repeats when compared to normal tissue - this is called microsatellite instability (MSI). Approximately 90% of CRCs occurring in individuals with LS exhibit MSI. Approximately 15% of sporadic cancers (not associated with LS) also exhibit MSI.
Table 1. Significant lifetime cancer risks for individuals who have inherited a mutation in the LS genes, MLH1 and MSH2, as compared to the general population. Risks for other MMR genes (MSH6, PMS2) are lower.

<table>
<thead>
<tr>
<th>Cancer type</th>
<th>Lynch syndrome lifetime cancer risk in a carrier of a MLH1 or MSH2 gene mutation</th>
<th>General Population lifetime cancer risk &lt; 70 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon</td>
<td>52-82% 44-61 years</td>
<td>5.5%</td>
</tr>
<tr>
<td>Endometrium</td>
<td>25-60% 48-62 years</td>
<td>2.7%</td>
</tr>
<tr>
<td>Stomach</td>
<td>6-13% 56 years</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Ovary</td>
<td>4-12% 42.5 years</td>
<td>1%</td>
</tr>
</tbody>
</table>

**SCREENING AND SURVEILLANCE**

For patients who have a known mutation in a LS gene, the genetics healthcare provider or oncologist should provide recommendations specific to the patient and his/her family history.

In general, for **high risk** individuals with MLH1 or MSH2 mutations and their first degree relatives who have not had genetic testing:

Colon Cancer: Colonoscopy every 1-2 years beginning between ages 20 and 25 or 2-5 years prior to the earliest diagnosis if that diagnosis was made before age 25 years, whichever is earlier.

Endometrial and Ovarian cancer: There is no specific screening for endometrial or ovarian cancer. Women should be educated about the symptoms of endometrial cancer. Prophylactic hysterectomy and bilateral salpingooophorectomy (BSP) is a risk-reducing option that women who have completed childbearing can consider.

Other Extracolonic cancers: Family history dependent. Recommended screening for urinary tract cancer is consideration of annual urinalysis starting at 25-30 years.

CRC screening for **intermediate risk** individuals is dependent on family history. For a person with a:

- 1st degree relative with CRC diagnosis <50 years or two 1st degree relatives with CRC at any age - Colonoscopy at age 40 or 10 years younger than the youngest CRC diagnosis, repeat 3-5 yearly
- 1st degree relative with CRC diagnosis ≥50 years - Colonoscopy at age 50 or 10 years younger than the youngest CRC diagnosis, repeat 5 yearly
- 2nd degree relative with CRC diagnosis <50 years - Colonoscopy at age 50, repeat dictated by findings

For patients who are at **general population risk**, including those who have tested negative for a familial CRC gene mutation, recommendations should follow provincial guidelines, i.e. Fecal Occult Blood Test every two years from age 50.

See [www.gecko-cego.ca](http://www.gecko-cego.ca) for the full GEC-KO Messenger on Lynch Syndrome for more details and how to contact your local genetics centre or hereditary cancer program.


Authors: S Morrison MS CGC, JE Allanson MD FRCPC and JC Carroll MD CCFP

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**CHROMOSOMAL MICROARRAY (CMA)**

**Bottom line:** Chromosomal microarray (CMA) is a high resolution genetic test to assess very small gains and losses (copy number variants) of genomic information in an individual. CMA should be considered for clinical presentation of:

- isolated autism spectrum disorder (ASD) or ASD plus other findings
- isolated global developmental delay or intellectual disability
- multiple congenital anomalies in the absence of a syndrome diagnosis
- unusual physical features (dysmorphisms)
- any combination of the above

CMA is not appropriate if a single gene disorder (e.g. Duchenne muscular dystrophy) or an aneuploidy (e.g. Down syndrome, trisomy 18) is suspected. It is not appropriate for couples experiencing multiple miscarriages or infertility.

Identifying the underlying etiology of an individual’s intellectual challenges and/or congenital anomalies is important for many reasons including counselling (e.g. family planning and prenatal testing, prognosis), providing access to appropriate resources, and alleviating psychological stress by ending the parental diagnostic odyssey.

**What is CMA?**

Chromosomal microarray (CMA) is a technology used to determine if there are small extra (micro-duplication) or missing (micro-deletion) pieces of genetic information. These gains and losses are called copy number variants (CNVs). A CNV can be: of no medical consequence; pathogenic resulting in physical and/or intellectual consequences; or protective against disease (e.g. HIV infection). The contribution of CNVs to common, complex diseases, such as diabetes, is less well understood.

Identifying the underlying etiology of an individual’s intellectual disabilities and/or congenital anomalies ends the diagnostic odyssey and eliminates other unnecessary diagnostic tests. Additionally, diagnosis can: facilitate access to needed services; empower families by knowing the underlying cause of a relative’s disorder; identify associated medical risks; facilitate more accurate recurrence-risk counselling; and allow for targeted testing of at-risk family members.

A microarray is a small glass slide on which thousands of genes are arrayed. Using a conventional DNA hybridization process, DNA probes are attached (hybridized) with differentially-labelled DNA - patient (green) and control/reference (red) - to reveal CNVs (gains and losses) at a much higher resolution than routine karyotype (chromosome analysis). In a normal situation, each probe on the array should hybridize equally to test (green) and control (red) DNA. This will produce a yellow signal. Extra pieces of DNA produce a green signal and missing pieces produce a red signal. The slide is scanned and images analyzed by computer.

Figure 1. CMA.
RED FLAGS TO CONSIDER MICROARRAY TESTING OR GENETIC CONSULTATION

⚠️ Isolated autism spectrum disorder (ASD)
  • Any individual with autistic features should first be assessed to make a definitive diagnosis, usually using tools such as ADOS and ADI
    - Autism Diagnostic Observation Schedule (ADOS) is an instrument for diagnosis and standardized assessment of autism. Autism Diagnostic Interview (ADI) is a companion instrument.
  • If autism is confirmed, a genetics referral should be considered
  • The genetics assessment will look for physical features (see those below) that might point to a syndrome or specific single gene disorder

⚠️ ASD- “Plus” is ASD accompanied by any of the findings below:
  A. Microcephaly OR macrocephaly
  B. Failure to thrive OR obesity
  C. Short stature OR overgrowth
  D. Dysmorphic features
  E. Congenital malformations
  F. Seizures
  G. Pigmentary changes suggestive of Tuberous Sclerosis on Wood’s lamp examination

⚠️ Isolated global developmental delay or intellectual disability without ASD or any findings listed above

FAMILY HISTORY RED FLAGS TO CONSIDER GENETIC TESTING

⚠️ A close relative with a known CNV related to a clinically significant physical and/or intellectual disability

When referring to Genetics for a positive family history include as much information about the affected family members as possible and encourage your patient to seek medical records and documentation.

WHAT DOES THE GENETIC TEST RESULT MEAN?

There are three possible results when ordering CMA. Patients should be counselled about all possible outcomes.

1. Normal
   • Excludes a micro-deletion/micro-duplication (CNV) within the limits of resolution of the test (typically very high)
     - This does not exclude a syndrome caused by a mutation within a single gene or detect a balanced translocation
   • A referral for genetic consultation should be considered so that additional genetic testing, depending on the patient’s presentation, may be offered

2. Pathogenic micro-deletion or micro-duplication (CNV)
   • CNV previously described and associated with a known abnormal phenotype
   • Depending on the finding, parental testing and/or additional medical surveillance may be indicated

3. Variation of unclear clinical significance (VUS)
   • Not every CNV in the genome is pathogenic
   • A variant that has not been described in the literature is challenging to interpret. Knowledge of parental status will determine whether or not the CNV is familial, and less likely to be pathogenic, or de novo (new in the affected individual) and more likely pathogenic
   • Parental samples should be obtained and analysed, then refer to genetics, if not already initiated

See www.gecko-cego.ca for the full GEC-KO Messenger on CMA and how to connect to your local genetics centre.


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**Bottom line:** NIPT is a screening test to prenatally detect Down syndrome and other aneuploidies. NIPT measures fetal DNA that is circulating in maternal blood to determine if there is a higher or lower than expected quantity of particular DNA sequences on select chromosomes. NIPT has higher sensitivity and specificity for Down syndrome and trisomy 18 than current screening tests – First Trimester Screening (FTS)/Integrated Prenatal Screening (IPS)/ Maternal Serum Screening (MSS) - however it is not considered to be diagnostic. Positive results should be confirmed by diagnostic testing (amniocentesis or chorionic villus sampling). Currently, NIPT is only validated in high-risk populations (e.g. advanced maternal age, positive FTS/IPS/MSS, ultrasound abnormality, previous aneuploidy, pregnancies conceived by reproductive technologies). In Canada, NIPT is not covered by provincial health plans. Prices vary by company (795$-1,200$).

**WHAT IS NIPT?**

Non-invasive prenatal testing (NIPT) is a highly sensitive and specific way to screen for particular chromosome aneuploidies (an abnormal chromosome number (extra or missing)):

- trisomy (an extra copy of a chromosome) 13, 18 and 21/Down syndrome
- trisomy of sex chromosomes (XXX, XXY, XYY) and Turner syndrome/Monosomy X
- triploidy (an extra copy of all the chromosomes i.e. 3 sets not 2 sets)

NIPT measures circulating cell free fetal DNA (ccfDNA) that is present in maternal blood. ccfDNA comprises approximately 10% of DNA in maternal blood and the amount increases with gestational age. Analysis of ccfDNA can determine if there is a normal, higher or lower than expected quantity of particular DNA sequences found on select chromosomes (13, 18, 21, X, Y). **It is a non-invasive test performed on a maternal blood sample that poses no risk to pregnancy.** Testing can be performed as early as 9 weeks’ gestation. A dating ultrasound is required prior to drawing the blood to ensure viability, an accurate gestational age and to exclude multiple pregnancies.

A series of NIPT validation studies have demonstrated high pick-up rates/sensitivity (which are company-specific) for the detection of Down syndrome (sensitivity 99-100% with false positive rates ~0.1%), trisomy 18 (sensitivity 97-100%), trisomy 13 (sensitivity 79-92%) and sex chromosome differences (sensitivity approximately 94-99% with some companies). A number of women (<6%) have been required to have repeat blood draws due to initial test failure.

At the present time, it is recommended that all women be offered prenatal screening, using either FTS, IPS or MSS. If a woman is screen positive or at high risk for other reasons (see Red Flags below), NIPT may be considered as a secondary screen of higher sensitivity if she is willing to pay for the test. **NIPT is not a replacement for diagnostic prenatal testing.** A positive NIPT result should be confirmed by diagnostic testing (amniocentesis or chorionic villus sampling [CVS]). The expected benefit of NIPT will be fewer women undergoing secondary invasive diagnostic tests associated with a risk of pregnancy loss.

NIPT is ordered by a healthcare professional. Some genetics centres are counselling patients about this testing option, and some are also organizing testing for patients who have already been referred because of a high risk indication. All patients should have pre- and post-test counselling to ensure informed decision making. Currently, NIPT is a self-pay option. Prices vary by company (795-1,200$).
**RED FLAGS TO CONSIDER GENETIC TESTING OR GENETIC CONSULTATION**

NIPT has been validated for use in women determined to be at high risk of having a fetus with certain aneuploidies. Consider discussing NIPT as an option with women who:

- Are of advanced maternal age
- Have had a previous aneuploidy pregnancy
- Have a personal history of sex chromosome aneuploidy, i.e. Turner syndrome (mosaic), 47, XXX
- Have an abnormal serum screen i.e. FTS/IPS/MSS
- Have an abnormal ultrasound finding such as increased nuchal translucency or cystic hygroma
- Have a pregnancy conceived via reproductive technologies

Eligibility is company-specific.

NIPT **has not yet been validated** in low risk women, triplets or other higher order multiple pregnancies, or in pregnancies conceived with egg donation.

**WHAT DOES THE GENETIC TEST RESULT MEAN?**

Depending on the company, results will be reported differently and may be worded as: positive or negative; aneuploidy detected, no aneuploidy detected or aneuploidy suspected/ borderline value; or high-risk or low risk.

Results typically take approximately 8-10 days.

**If the result is negative**, this is reassuring, however NIPT **cannot**:

- completely rule out aneuploidy
- detect aneuploidy other than chromosomes 13, 18, 21, X and Y
- detect single gene conditions
- detect congenital anomalies

Your patient should still be offered:

- maternal serum alpha-fetoprotein (MS-AFP) to screen for open neural tube defect (ONTD), as NIPT does not screen for this physical anomaly
- a fetal morphology scan at 18-20 weeks’ gestation

**If the result is positive**, follow-up genetic counselling is indicated and confirmation by diagnostic testing should be offered. The Society of Obstetricians and Gynecologists of Canada (SOGC) and numerous North American Genetics societies/colleges recommend that no irrevocable obstetrical decisions should be made in pregnancies with abnormal NIPT results without confirmatory invasive testing (amniocentesis or CVS).

See [www.gecko-cego.ca](http://www.gecko-cego.ca) for the full GEC-KO Messenger on NIPT and how to connect to your local genetics centre.

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Bottom line: Direct-to-consumer genetic testing (DTC-GT) is over-the-counter genetic testing available online to consumers through private companies. Generally, results report an individual’s risk to develop a medical condition as being below average/low, average/general population, and above average/high based on genome wide association studies (GWAS). Results may provide medically useful information for consumers and potentially provide support and motivation for lifestyle changes (e.g. weight loss, smoking cessation) or even more vigilant surveillance (e.g. breast cancer screening), reveal carrier status of single gene conditions (e.g. cystic fibrosis), effectiveness and side-effect risk of certain pharmaceuticals, in addition to medically irrelevant information (e.g. curly hair). Currently, DTC-GT is not regulated or accountable to an appropriate governing body.

Family health history-based risk assessment is still the gold standard in initial assessment for heritable conditions.

WHAT IS DTC?

Direct-to-consumer genetic testing (DTC-GT), also referred to as personal genome testing, is generally offered with the promise of providing predictive genetic risk assessment for a variety of health conditions (i.e. diabetes, cancer, obesity) and information regarding response to and/or side-effect risk of certain pharmaceuticals (i.e. clopidogrel, statins).

DTC-GT uses data generated from genome-wide association studies (GWAS). GWAS are case-control studies which examine many common variations in our genetic code (single nucleotide polymorphisms [SNPs]). They compare large groups of individuals (unaffected controls versus individuals with symptoms of a specific disease) in an attempt to distinguish between non-harmful changes in the DNA code and pathogenic, disease causing/predisposing changes. SNPs (pronounced ‘snips’) are the most common type of genetic variation. Each SNP represents a difference in a single DNA building block, a nucleotide. SNPs occur normally in an individual’s genome about once in every 300 nucleotides, and so there are about 10 million SNPs in the human genome.

DTC-GT uses odds ratios and relative risks to categorize an individual as at increased risk (higher than average), average, or at decreased risk (lower than average). DTC-GT can also screen for single gene disorders (e.g. cystic fibrosis, HFE-associated hemochromatosis). Additionally, DTC-GT testing can uncover medically irrelevant information such as bitter taste perception or curly hair.

Generally, DTC-GT is available online to anyone for a cost. Genetic testing for DTC-GT is usually performed on a saliva sample.

Appropriate pre- and post-test counselling is rarely offered by the DTC-GT company. Ideally, it should be carried out so that the consumer is informed of what the results might reveal (e.g. risk of multifactorial conditions that arise due to the combined contribution of genetic and environmental factors, carrier status of single gene conditions, including cancer predisposition syndromes) and the potential for results requiring additional medical follow-up not limited to behavioural modifications (e.g. increase exercise and smoking cessation, vigilant breast screening and discussion of prophylactic surgery as a result of a BRCA mutation). The implications for extended family members should be addressed.
WHAT DOES THE GENETIC TEST RESULT MEAN?

While there are limited data to support the clinical validity (ability to predict clinical outcome) and utility (the likelihood of improving patient outcome), some consumers might benefit from DTC-GT as results may:

- Encourage positive behaviour modifications (e.g. increase exercise, smoking cessation)
- Provide useful information for medication choice and/or dose, or management
- Provide information to individuals who have no or limited information about their family history (e.g. an individual who was adopted)
- Reveal carrier status of a genetic condition that could have implications for family planning

Caution when interpreting DTC-GT should be exercised as:

- DTC-GT does not take into account numerous factors important when interpreting genetic test results such as age, family history, lifestyle (e.g. smoking, obesity) and other environmental factors that are a significant contribution to common complex disease development
- Family health history-based risk assessment is still the gold standard in the initial assessment for heritable conditions

The impact on a publicly funded healthcare system of the result of a privately obtained test that suggests additional follow-up (i.e. blood tests, colonoscopy), which is not otherwise indicated, is unknown. Referral to a specialist or confirmation of test results in a clinical laboratory may be indicated in some circumstances to clarify appropriate surveillance and management. Additionally, “misattributed equivalence” is a great concern associated with personalised genome testing. There is a fear that if a DTC-GT test were to indicate a lower than average lifetime risk for a certain condition, when family history indicated a much higher risk, a consumer could be falsely reassured and not be as vigilant about medical interventions indicated by family history. This phenomenon speaks to the need for knowledgeable healthcare provider involvement in pre- and post-test counselling.

On the other hand, recognizing the limitation of self-reported family history (incorrect or incomplete information), there may be potential for DTC-GT to add to risk interpretation in some situations (e.g. response to and/or side effect risk of certain pharmaceuticals).

Currently no DTC-GT is approved by Health Canada or the U.S. Federal Drug Administration (FDA). While several professional organizations have released position papers regarding standard quality management systems, there is currently no regulation. Staff performing testing, analysis and interpretation of results may not be certified or licenced by an appropriate governing body.

See www.gecko-cego.ca for more details and how to connect to your local genetics centre.

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